

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#18
3/19/02
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In re application of

Tohru YASUKOHCHI, et al.

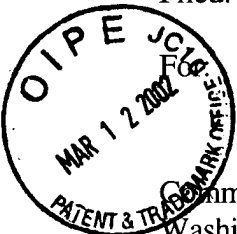
Appln. No.: 09/367,642

Group Art Unit: 1712

Confirmation No.: Unassigned

Examiner: Buttner, D.

Filed: August 19, 1999



OXIRANE DERIVATIVE AND PROCESS FOR THE PREPARATION THEREOF

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

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Sir:

I, Chika Ito, declare and state as follows:

I graduated from Osaka University of Pharmaceutical Sciences in 1988, receiving a masters degree of Pharmaceutical Science. Since 1988, I have been employed by NOF Corporation.

I am a co-inventor of the invention described and claimed in the above-identified application.

I am familiar with the Office Action dated July 12, 2001, where claims 1-6 and 8-10 were rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent 4,967,016 to Kemp. Claims 1-4, 7, 8 and 11-15 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,605,976 to Martinez et al or JP 8-165343 (JP '343). Claims 1-15 were further rejected under 35 U.S.C. § 103(a) as being unpatentable over Martinez et al or JP '343 in combination with Kemp.

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The Examiner considered that the prior art products inherently meet the claimed purity requirements. Alternatively, because the prior art is said to teach reducing the water content to achieve a pure alkoxyated compound, the Examiner considered that it would have been obvious to reduce the water content to a level needed to meet the claimed purity requirements.

I report below on comparative experimentation that was conducted by myself or under my direct supervision.

As described herein, various oxirane derivatives were prepared following the procedure of Kemp and evaluated by GPC and TLC relative to the purity requirements of present claims 1-3. In Experiment 1 (Compound A), the Kemp catalyst (barium phosphate) was used to synthesize an oxirane derivative from a low-molecular compound (methanol). In Experiment 2, Example 1 of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) was repeated to synthesize an oxirane derivative from a higher alcohol C₁₂-C₁₃ mixture used as a starting material. Both a lower adduct compound (Compound B of Experiment 2-1) and a higher adduct compound (Compound C of Experiment 2-2) were prepared and tested. In Experiment 3, the process of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) was used to synthesize an oxirane derivative from benzyl alcohol (a C₇ hydrocarbon). Both a lower adduct compound (Compound D) and a higher adduct compound were prepared (Compound E).

Experiment 1 below demonstrates that when the Kemp catalyst (barium phosphate) is used to synthesize an oxirane derivative from a low-molecular compound such as methanol (Compound A), a high-molecular oxirane derivative having an average adduct number of from

20 to 900 required by claim 1 cannot be obtained. Also, the resulting oxirane derivative does not meet the GPC and TLC requirements of claim 1. This was the case even though even though (in Experiment 1) the maximum amount of ethylene oxide possible was forced into the reaction system. Experiment 2 demonstrates that the process of Kemp (barium phosphate catalyst, higher alcohol C₁₂-C₁₃ mixture used a starting material, and heating in a nitrogen stream to remove water) also does not provide an oxirane derivative of the requisite purity. Both a lower adduct compound (Compound B of Experiment 2-1) and a higher adduct compound (Compound C of Experiment 2-2) were prepared and tested. Experiment 3 demonstrates that the process of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) applied to a C₇ hydrocarbon used a starting material, also cannot provide an oxirane derivative having the claimed adduct number of from 20 to 900. This was still the case even though (in Experiment 3) the maximum amount of ethylene oxide possible was forced into the reaction system. (Compound E).

COMPARATIVE EXPERIMENTATION

EXPERIMENT 1

Synthesis of the compound of Example 2 of the present invention (pages 31-33 of the specification) was attempted using the barium phosphate catalyst of Kemp and dehydrated methanol, and the purity of the compound thus synthesized was evaluated.

1) Preparation of Catalyst (Barium Phosphate) Following Example 2 of Kemp

Into a 5-L four-neck flask equipped with a stirrer and a thermometer were introduced 30.0 g (0.1584 mol) of barium hydroxide monohydrate and 3,000 mL of distilled water. The

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contents were stirred for 1 hour to completely dissolve the solid. Subsequently, 12.2 g of 85% phosphoric acid solution (phosphoric acid, 0.1056 mol) was diluted with 200 mL of distilled water, and the dilution was wholly transferred to a dropping funnel and dropped into the four-neck flask over a period of 2 hours. After completing the addition of the whole dilution, the mixture was continuously stirred for an additional 2 hours at room temperature. The whole resultant reaction mixture was filtered under reduced pressure with a Buchner funnel. The white crystals remaining on the funnel were washed by gradually pouring 1,200 mL of distilled water on the crystals on the funnel with filtration. After the whole distilled water had been poured, the suction was further continued until filtrate dripping stopped. The crystals thus obtained were wholly placed on a laboratory dish, which was placed in a vacuum dryer and held under vacuum at 120°C. After the degree of vacuum had reached 20 mmHg, the vacuum drying was continued for an additional 3 hours. Thus, 28.9 g (0.048 mol) of barium phosphate ($\text{Ba}_3(\text{PO}_4)_2$) was obtained.

2) Synthesis of Compound of Example 2

The catalyst obtained in 1) was used to attempt synthesis of the compound of Example 2 of the invention (pages 31-33 of the specification).

A 5-L autoclave equipped with a stirrer, injection pipe, thermometer, and nitrogen gas blowing tube was dried at 130°C for 3 hours at a reduced pressure of 50 mmHg or lower. Into this autoclave were introduced 110 g (3.4375 mol) of dehydrated methanol (manufactured by Kanto Chemical Co., Ltd.; water content, 98 ppm) and 2.50 g (0.0042 mol) of the barium

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phosphate prepared in 1).¹ After the atmosphere in the autoclave was replaced with nitrogen, the contents were heated to $85\pm 5^{\circ}\text{C}$.² At this time, the pressure was about 0.4 MPa. Since the working pressure for this autoclave was 0.6 MPa, ethylene oxide was forced thereinto little by little at $85\pm 5^{\circ}\text{C}$ for safety. However, at the time when the ethylene oxide which had been forced thereinto amounted to 105 g, the pressure inside the autoclave reached 0.6 MPa. The forcing was hence stopped, and the reaction mixture was continuously stirred at that temperature. Although stirring was continued at that temperature for 16 hours thereafter, the pressure did not decrease. Because of this, the reaction was judged no longer to be proceeding, and the temperature was lowered to room temperature. The whole reaction mixture was discharged from the autoclave and placed in a beaker.

The discharged reaction mixture was wholly placed in an evaporator and concentrated under vacuum on a water bath having a temperature of $45\pm 2^{\circ}\text{C}$.

Ten grams of alkali adsorbent KYOWORD 700 (manufactured by Kyowa Chemical Industries, Ltd.) was added to the concentrate. This mixture was stirred at the above temperature

¹ In Experiment 1, the same dehydration method as that employed by Kemp could not be used. This is because methanol has a lower boiling point than water and, hence, use of the thermal dehydration employed by Kemp would result in evaporation of the methanol as a starting material in preference to water evaporation. Because of this, dehydrated methanol having a low water content was used as a starting material in this Experiment.

² The reason why the temperature could not be sufficiently elevated in Experiment 1 is that methanol has a high vapor pressure as stated above. In view of this, a $\text{C}_{12}/\text{C}_{13}$ mixed alcohol such as that employed by Kemp was used as a starting material in Experiment 2 so that a higher temperature could be used.

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for 30 minutes and then wholly filtered under reduced pressure. Thus, 132 g of a reaction product Compound A was obtained.

The reaction product Compound A thus obtained was analyzed by gel permeation chromatography (GPC).

The GPC conditions used were as follows.

GPC system: SHODEX GPC SYSTEM-11

Differential refractometer: SHODEX R1-7I

GPC column: three SHODEX KF804L (Φ 8 mm x 300 mm) columns connected in series

Column temperature: 40°C

Developer: tetrahydrofuran; flow rate, 1 mL/min

Sample concentration: 0.1% solution in THF; sample injection amount, 0.1 mL

The chromatogram obtained is shown in attached Fig. 1.

Compound A obtained in this Experiment was outside the scope of the invention. For reference, however, this compound was analyzed for the properties specified in the claims.

From the resultant data table, the following were found. The retention time at the elution starting point was 28.508 minutes. The retention time at Ptop was 31.725 minutes. The retention times at the two points where the height of the elution curve from PbaseL was one-fifth the height of PtopH were 31.383 minutes and 31.975 minutes, respectively. The retention time

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at the elution end point was 32.150 minutes. Furthermore, Parea was 255605, PareaM was 145536, and PareaH was 105850.

From these results, the following values were calculated.

$$\text{PareaM/Parea} = 0.569$$

$$\text{PareaH/Parea} = 0.414$$

The results further showed that PtopMw was 79, PMmw/mn was 1.0194, and PtopEOmol was 1.07. Consequently, the following equation holds.

$$\text{PMmw/mn} - \{1 + \text{PtopEOmol}/(1 + \text{PtopEOmol})^2\} = -0.230$$

With respect to TLC, the Compound A was unable to be separated and detected under the TLC conditions specified in the claims. This is because the molecular weight of Compound A was too low.

DISCUSSION 1

An examination of the GPC chart reveals that the reaction product Compound A was constituted of adducts of from 1 to 4 mol of ethylene oxide with methanol.

It can be seen from the above that when the Kemp catalyst is used to synthesize an oxirane derivative from a low-molecular compound such as methanol (Compound A), a high-molecular oxirane derivative having an average adduct number of from 20 to 900 required by claim 1 cannot be obtained. Also, the resulting oxirane derivative does not meet the GPC and TLC requirements of claim 1.

EXPERIMENT 2

In Experiment 1, the use of methanol resulted in an increase in autoclave pressure due to the vapor pressure of methanol, making it impossible to use a higher reaction temperature. On the assumption that the reaction did not proceed due to this limitation on reaction temperature, higher alcohols such as those used by Kemp were used as a starting material to attempt synthesis of a high-molecular oxirane derivative.

EXPERIMENT 2-1

Into a 5-L autoclave which had been dried in the same manner as in Experiment 1 were introduced 110 g (0.567 mol) of Dovanol 23 (manufactured by Mitsubishi Chemical Corp.; C12 alcohol content, about 40%; C13 alcohol content, about 60%; degree of branching, about 20%; av. Mw, 194; Lot No. G-027L) and 2.50 g (0.0042 mol) of the barium phosphate prepared in Experiment 1. In a nitrogen gas stream, the autoclave was held open at $145\pm 5^{\circ}\text{C}$ (although Kemp used an autoclave temperature of 155°C , the autoclave temperature could not be further increased because the steam supplied to the autoclave jacket was already at the highest allowable pressure) for 20 minutes to distill off water. Subsequently, the blow valve of the autoclave was closed and the pressure inside the autoclave was elevated to 0.1 MPa with nitrogen. Ethylene oxide was then gradually forced into the autoclave at $145\pm 5^{\circ}\text{C}$ while regulating the forcing rate so that the pressure inside the autoclave was kept at 0.6 MPa or lower.

Thus, 180 g (4.1 mol) of ethylene oxide was forced into the autoclave over a period of 3 hours. Thereafter, the autoclave was kept at that temperature for further 1.5 hours, and the

temperature was then lowered to 50°C. While that pressure inside the autoclave was maintained, the resultant reaction mixture was discharged through the bottom valve and placed in a beaker exactly in an amount of 251.3 g.³

To the reaction mixture obtained was added 10 g of KYOWORD 700. This mixture was stirred at 60°C for 30 minutes and then filtered under reduced pressure. Thus, 232 g of a reaction product Compound B was obtained, corresponding to Example 1 of Kemp. A gel permeation chromatogram for the reaction product Compound B thus obtained is shown in attached Fig. 2.

EXPERIMENT 2-2

Subsequently, synthesis of a compound according to the invention was attempted under conditions according to the Kemp process (barium phosphate catalyst, higher alcohol C₁₂-C₁₃ mixture used as a starting material, and heating under reduced pressure to remove water) in the following manner. The autoclave was reheated to 145±5°C, and ethylene oxide was continuously forced thereinto under conditions of 145±5°C and 0.6 MPa or lower. At the time when the ethylene oxide which had been fed after the discharge amounted to 82 g (1.86 mol), the pressure did not readily decrease from 0.6 MPa. Because of this, the rate of ethylene oxide forcing became exceedingly low, and further forcing 277.1 g (6.3 mol) of ethylene oxide took about 53 hours.

³ In Experiment 2, the Kemp process (heating under reduced pressure and in the presence of a barium phosphate catalyst) was used for synthesis in Experiment 2-1. However, the number of moles of ethylene oxide added was small (in contrast to 20 to 900 mols in the invention). Experiment 2-2 was hence carried out.

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After the ethylene oxide had been wholly forced into the autoclave, the reaction mixture was continuously stirred at that temperature for further 2 hours. The temperature of the autoclave was then lowered to 80°C, and the whole reaction mixture was discharged from the autoclave and placed in a beaker. To the reaction mixture thus obtained was added 10 g of KYOWORD 700. This mixture was stirred at 80°C for 30 minutes and then filtered. Thus, 312 g of a reaction product C was obtained.

A gel permeation chromatogram for the reaction product Compound C thus obtained is shown in attached Fig. 3.

Compounds B and C obtained in Experiment 2 were also outside the scope of the invention. For reference, however, these compounds were analyzed for the properties specified in the claims.

DISCUSSION 2: With Respect to Compound B

From the resultant data table, the following were found. The retention time at the elution starting point was 25.770 minutes. The retention time at Ptop was 28.200 minutes. The retention times at the two points where the height of the elution curve from PbaseL was one-fifth the height of PtopH were 27.640 minutes and 28.860 minutes, respectively. The retention time at the elution end point was 31.160 minutes. Furthermore, Parea was 717210, PareaM was 615760, and PareaH was 37714.

From these results, the following values are calculated.

$$\text{PareaM/Parea} = 0.859$$

$$\text{PareaH/Parea} = 0.053$$

The results further showed that PtopMw was 592, PMmw/mn was 1.0158, and PtopEOmol was 9.05. Consequently, the following equation holds.

$$\text{PMmw/mn} - \{1 + \text{PtopEOmol}/(1 + \text{PtopEOmol})^2\} = -0.074$$

Compound B was further analyzed by TLC. As a result, the main spot was found to have an Rf value of 0.744. Examination with a densitometer revealed that many by-product spots had appeared in a large amount. Although quantitative analysis by thin layer chromatography was hence difficult and precise calculation was impossible, the content of the main component in the reaction product was 88% or lower.

The gel permeation chromatogram of Fig. 2 shows that a relatively high-purity oxirane derivative is obtained by the Kemp process when the target compound is one in which a small

number of moles of ethylene oxide are added (Compound B). However, the results of the analysis by thin layer chromatography show that the purity of the derivative obtained by the Kemp process was far lower than that of the oxirane derivative of the invention. More particularly, Compound B did not meet the TLC requirements of claim 1.

DISCUSSION 3: With Respect to Compound C

From the resultant data table, the following were found. The retention time at the elution starting point was 16.880 minutes. The retention time at Ptop was 23.975 minutes. The retention times at the two points where the height of the elution curve from PbaseL was one-fifth the height of PtopH were 23.520 minutes and 24.390 minutes, respectively. The retention time at the elution end point was 25.260 minutes. Furthermore, Parea was 710195, PareaM was 478317, and PareaH was 216520.

From these results, the following values were calculated.

$$PareaM/Parea = 0.674$$

$$PareaH/Parea = 0.305$$

The results further showed that PtopMw was 5214, PMmw/mn was 1.0119, and PtopEOmol was 114.09. Consequently, the following equation holds.

$$PMmw/mn - \{1 + PtopEOmol/(1 + PtopEOmol)^2\} = 0.003$$

Compound C was further analyzed by TLC. As a result, the main spot was found to have an Rf value of 0.487. Examination with a densitometer revealed that although quantitative

analysis by thin layer chromatography was difficult and precise calculation was impossible, the content of the main component in the reaction product was 81% or lower.

Fig. 3 shows that the reaction product contained a large amount of impurities. Although what these impurities were attributable to is unclear, it is presumed that in producing a high-molecular target compound by the Kemp process, side reactions such as, e.g., decomposition of a reactant and esterification with the barium phosphate used as the catalyst occur due to the low activity of the Kemp catalyst.

EXPERIMENT 3

Synthesis of the compound of Example 5 of the present invention (pages 38-40 of the specification) from benzyl alcohol (a C₇ hydrocarbon) was attempted using the barium phosphate catalyst of Kemp and heating in a nitrogen stream to remove water, and the purity of the compound thus synthesized was evaluated.

1) Synthesis of the compound of Example 5 following the process of Kemp

Into a 5 L autoclave in which the air within had been dried in the same manner as in Experiment 1 were charged 86.4 g (0.8 mol) of benzyl alcohol (reagent produced by KANTO KAGAKU CORPORATION) and 1.96 g (0.0033 mol) of barium phosphate prepared in Experiment 1-1). The reaction system was then kept open at a temperature of $145 \pm 5^{\circ}\text{C}$ (The reaction system could not be kept at a temperature of higher than $145 \pm 5^{\circ}\text{C}$ because the vapor pressure in the autoclave jacket was about 0.4 MPa) in a stream of nitrogen gas for 20 minutes during which the resulting water was distilled off. Subsequently, with the blow-off valve of the

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autoclave closed, nitrogen was pressed into the autoclave to raise the inner pressure of the autoclave to 0.1 MPa. Ethylene oxide was then gradually pressed into the autoclave at a temperature of $145 \pm 5^{\circ}\text{C}$ while the amount of ethylene oxide to be pressed thereinto was being controlled such that the inner pressure of the autoclave reached 0.6 MPa or less.

282 g (6.4 mol) of ethylene oxide was thus pressed into the autoclave in 3 hours. The content of the autoclave was then further kept at the same temperature for 1.5 hours. Subsequently, the temperature of the autoclave was lowered to 50°C . The reaction solution was then withdrawn from the autoclave through the bottom valve in an accurate amount of 290 g while the pressure in the autoclave was kept constant.

To the reaction solution thus obtained was then added 10 g of KYOWORD 700. The mixture was stirred at a temperature of 60°C for 30 minutes, and then filtered under reduced pressure to obtain 274 g of Compound D (adduct number of 7.95), following Kemp's example. The chromatogram of Compound D thus obtained is shown in Fig. 4.

Subsequently, in an attempt to synthesize the compound of the present invention (having an adduct number of 20 or higher) under Kemp's conditions, the autoclave was again heated to a temperature of $145 \pm 5^{\circ}\text{C}$ where ethylene oxide was then pressed thereinto at a pressure of 0.6 MPa or less. However, when ethylene oxide was charged into the autoclave in an amount of 57 g (1.3 mol), the pressure was no longer reduced from 0.6 MPa. The pressing of ethylene oxide was then suspended. The content of the autoclave was then stirred at the same temperature for 24 hours.

Even after 24 hours of ripening, no pressure reduction was observed. Thus, it was judged that the reaction would no longer proceed. The reaction was then suspended.

The temperature of the autoclave was lowered to 50°C where the whole of the reaction solution was then withdrawn therefrom and placed into a beaker. To the reaction solution thus obtained was then added 10 g of KYOWORD 700. The mixture was stirred at a temperature of 60°C for 30 minutes, and then filtered to obtain 116 g of Compound E (adduct number of 13.82).

A GPC chromatogram of Compound E thus obtained is shown in Fig. 5.

Compounds D and E thus obtained from a C₇ alcohol as a starting material and following the procedure of Kemp (barium phosphate catalyst, and heating in a stream of nitrogen gas to remove water) were analyzed as specified in the claims of the present application. As shown below, Compounds D and E obtained in Experiment 4 were also outside the scope of the invention.

Discussion 4: With respect to Compound D

The data table shows that the retention time at the elution starting point was 26.983 minutes, the retention time P_{top} was 28.775 minutes, the retention time at the two points where the height of the elution curve from PhaseL is one-fifth of the height of P_{topH} were 28.217 minutes and 29.425 minutes, respectively, the retention time at the elution end point was 30.917 minutes, P_{area} was 1,061,985, P_{areaM} was 978,362, and P_{areaH} was 39,765.

From these results the following values were calculated:

$$P_{areaM}/P_{area} = 0.921$$

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$$\text{PareaH/Parea} = 0.037$$

The results further show that PtopMw was 458, PMmw/mn was 1.0153, and PtopEOmol was 7.95. Consequently, the following equation holds.

$$\text{PMmw/mn} - \{1 + \text{PtopEOmol}/(1 + \text{PtopEOmol})^2\} = -0.084$$

Compound D was further analyzed by TLC. As a result, the main spot was found to have an Rf value of 0.679. Analysis with a densitometer revealed that the content of the main component and the by-products were 96.20% and 3.80%, respectively.

As can be seen in Fig. 4, when the target compound is one in which a small number of moles of ethylene oxide (i.e., adduct number of 7.95 outside the scope of claim 1) are added, a relatively high purity oxirane derivative is obtained by the Kemp process. However, the results of the analysis by thin layer chromatography show that the purity of the derivative obtained by the Kemp process was far lower than that of the oxirane derivative required by the present claims.

Discussion 5: With Respect to Compound E

The data table shows that the retention time at the elution starting point was 26.058 minutes, the retention time Ptop was 27.767 minutes, the retention time at the two points where the height of the elution curve from PhaseL is one-fifth of the height of PtopH were 27.308 minutes and 28.250 minutes, respectively, the retention time at the elution end point was 29.717 minutes, Parea was 944,233, PareaM was 842,203, and PareaH was 55,302.

From these results the following values were calculated:

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$$\text{PareaM/Parea} = 0.892$$

$$\text{PareaH/Parea} = 0.059$$

The results further show that PtopMw was 716, PMmw/mn was 1.0099, and PtopEOmol was 13.82. Consequently, the following equation holds.

$$\text{PMmw/mn} - \{1 + \text{PtopEOmol}/(1 + \text{PtopEOmol})^2\} = -0.053$$

Compound E was further analyzed by TLC. As a result, the main spot was found to have an Rf value of 0.636. Analysis with a densitometer revealed that the content of the main component and the by-products were 94.70% and 5.30%, respectively.

As can be seen in Fig. 5, the reaction product thus obtained contained a higher molecular compound having an adduct number of 13.82, the proportion of which showed an increase from that of Fig. 4. Importantly, even in this case where the maximum amount of ethylene oxide possible was forced into the system (in an attempt to obtain a higher adduct number), the reaction product had an adduct number of 13.82 considerably less than the adduct number of 20-900 required by claim 1.

The results of the above Experiments are summarized in Table 1 below for comparison with the property ranges specified in the claims.

Table 1

	Average number of moles of ethylene oxide added	Gel permeation chromatography			Thin layer chromatography	
		PareaM/ Parea	PareaH/ Parea	A ¹⁾	Rf value	Purity of main spot (%)
Ranges in the claims	20-900 (claim 1)	≥0.85 (claim 1)	≤0.05 (claim 2)	≤0.02 (claim 3)	0.2-0.8 (claim 1)	≥98% (claim 1)
Compound A	1.07*	0.569	0.414	-0.230	Not detectable	not detectable
Compound B	9.05	0.859	0.053	-0.074	0.744	≤88%
Compound C	114.09	0.674	0.304	0.003	0.487	≤81%
Compound D	7.95	0.921	0.037	-0.679	0.679	96.20%
Compound E	13.82*	0.892	0.059	-0.053	0.636	94.70%

A¹⁾: $PM_{mw}/mm - \{1 + P_{topEO}mol/(1 + P_{topEO}mol)^2\}$

* Additional ethylene oxide could not be added.

The results of Table 1 show the following. Compound A (barium phosphate catalyst of Kemp, starting material: methanol) did not meet the GPC requirements of claims 1 and 2 and did not meet the TLC requirements of claim 1. Also, the average number of moles of ethylene oxide added therein was 1.07, which is outside the range of claim 1. Compound B (Kemp process, barium phosphate catalyst, heating in a stream of nitrogen gas to remove water and starting material: C₁₂-C₁₃ alcohol mixture) did not meet the GPC requirements of claim 2 and did not meet the TLC requirements of claim 1. Also, the average number of moles of ethylene oxide added therein was 9.05, which is outside the range of claim 1. Compound C (Kemp process,

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barium phosphate catalyst, heating in a nitrogen stream to remove water and starting material: C₁₂-C₁₃ alcohol mixture, number of moles of ethylene oxide added, 114.09), which had been synthesized so as to be within the adduct number range of the invention, was also outside the scope of the claims with respect to most of the purity requirements. Compound D (Kemp process, barium phosphate catalyst, heating in a nitrogen stream to remove water and starting material: C₇ alcohol) did not meet the TLC requirements of claim 1. Also, the average number of moles of ethylene oxide added therein was 7.95, outside the scope of claim 1. Compound E (Kemp process, barium phosphate catalyst, heating in a nitrogen stream to remove water and starting material: C₇ alcohol) which had been synthesized to incorporate the maximum amount of ethylene oxide possible, did not meet the GPC requirements of claim 2 and did not meet the TLC requirements of claim 1. Also, the average number of moles of ethylene oxide added therein was 13.82, outside the scope of claim 1.

EVALUATION OF TEST RESULTS

a. Differences in processing result in different end products

Kemp uses barium phosphate as a catalyst which is an essential element of his alkoxylation process (col. 5, lines 47-49, Example 1 at col. 10, lines 30-32, etc.). On the other hand, barium phosphate is not used in the present invention. In the present invention, the water content in the reaction system is more than 5 ppm, and alkali metal or alcoholate of alkali metal is used. The metallic sodium reacts with water present in the reaction system to form NaOH which also acts as a catalyst. This difference in processing provides for the preparation of oxirane derivatives having the requisite purity as defined in claim 1, which purity cannot be achieved by Kemp.

b. Method of water removal - Kemp

Kemp discloses lowering the water content by heating the mixture of the active hydrogen compound and the catalyst under reduced pressure (not higher than 100 Torr) (column 7, line 55). Also, Kemp states that the water content should not be more than 500 ppm, preferably not more than 200 ppm, to achieve such purpose (column 7, line 49). In practice (see, Example 1 at col. 10, lines 34-36), Kemp heats the reaction system "under a constant nitrogen sparge to drive off water".

However, Kemp's technique for removing water (either by heating under reduced pressure or heating in a nitrogen stream) is effective, and even then only marginally so, when the alcohol used as a starting material has a large number of carbon atoms and hence a boiling point considerably higher than that of water. On the contrary, if the alcohol used as a starting material

has a small number of carbon atoms (C_1 - C_7 of the invention) and therefore has a boiling point close to or lower than that of water, water cannot be effectively removed from the reaction system by heating under reduced pressure or by heating in a nitrogen stream (see, page 4, line 1 - page 5, line 4 of the specification).

c. Adduct number

Although Kemp suggests that the adduct number can be 30 or greater, Kemp never prepared such products. Furthermore, although Kemp did prepare products including compounds having an adduct number of 20 to 21 (see Example 10 of Kemp), the alkoxylate distribution of the end product was very broad having a molecular weight distribution outside the scope of claim 1. Also, a C_{11} - C_{12} alkanol mixture outside the scope of the present claims was used as a starting material (col. 18, lines 22-24). Kemp's method cannot provide a high molecular weight oxirane derivative having the requisite purity.

d. Summary of Test Results

Experiment 1 demonstrates that when the Kemp catalyst (barium phosphate) is used to synthesize an oxirane derivative from a low-molecular compound such as methanol (Compound A), a high-molecular oxirane derivative having the claimed adduct number of from 20 to 900 cannot be obtained. Also, the resulting oxirane derivative does not meet the GPC and TLC requirements of claim 1. Particularly, as shown in Table 1 above, Compound A had an average adduct number well outside the scope of claim 1 even though (in Experiment 1) the maximum amount of ethylene oxide possible was forced into the reaction system. This is presumably because the barium phosphate catalyst of Kemp has low activity such that the adduct number

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cannot be substantially increased when a low molecular compound (C_1 - C_7) is used as a starting material. Furthermore, Compound A had a GPC purity well outside the scope of claim 1. Also, Compound A could not be separated and could not be detected under the TLC conditions specified in claim 1.

Experiment 2 demonstrates that even when the process of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) is applied to a higher alcohol C_{12} - C_{13} mixture (which itself is outside the scope of claim 1), the resulting oxirane derivative does not have the required purity. Both a lower adduct compound (Compound B of Experiment 2-1) and a higher adduct compound (Compound C of Experiment 2-2) were prepared and tested. As shown in Table 1 above, Compound B (low adduct number outside the scope of the present claims) was relatively pure in terms of GPC analysis, but did not have a TLC purity of not less than 98% as required by claim 1. In any event, the adduct number of Compound B is outside the scope of claim 1 requiring addition of an average number of moles of oxirane groups of from 20 to 900. In Experiment 2-2, a higher molecular weight compound was prepared having an adduct number of about 114 within the scope of claim 1. However, the resulting Compound C also failed to meet the GPC and TLC purity levels required by claim 1.

Experiment 3 demonstrates that when the process of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) is applied to a C_7 hydrocarbon - benzyl alcohol (Compound D and E), a high-molecular oxirane derivative having the claimed adduct number of from 20 to 900 cannot be obtained. Also, the resulting oxirane derivative does not meet the TLC purity levels required by claim 1. Importantly, Kemp's process was unable to

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provide a product having an adduct number of at least 20 even when the maximum amount of ethylene oxide possible was forced into the reaction system (Compound E).

The above test results show that:

- (i) Kemp did not prepare an oxirane derivative having the purity required by claim 1,
- (ii) when the Kemp catalyst is used to synthesize an oxirane derivative from a low-molecular compound such as methanol, a high-molecular oxirane derivative having an adduct number of from 20 to 900 required by claim 1 cannot be obtained,
- (iii) even when the Kemp process is used to prepare a high-molecular oxirane derivative using a higher C₁₂-C₁₃ alcohol as a starting material (which itself is outside the scope of claim 1), the resulting compound does not meet the GPC and TLC requirements of claim 1, and
- (iv) when the Kemp process is used to prepare an oxirane derivative from a C₇ hydrocarbon, a high-molecular oxirane derivative having an adduct number of from 20 to 900 required by claim 1 cannot be obtained.

This is due to differences in the catalyst and process used for making the oxirane derivative, and the above test data shows that these differences are material to both the purity and adduct number of the end product as defined in present claim 1.

Regarding the Examiner's position that it would have been obvious to modify Martinez et al. or JP '343 to achieve oxirane derivatives having the requisite purity based on Kemp (teaching that it is important to keep water content low during the reaction to achieve a high purity product), the test data presented herein shows that Kemp's process cannot provide an


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oxirane derivative from a C₁-C₇ hydrocarbon having an adduct number of at least 20, let alone one meeting the GPC and TLC requirements of claim 1. Particularly, this is the starting material used by Martinez et al to prepare polyoxyalkaline derivatives containing carboxyl groups and by JP '343 to prepare polyoxyalkaline monoamines. If the starting material does not have the requisite purity, then the carboxyl or amine derivative does not have the desired purity. This is demonstrated in Examples 8 and 9 and Comparative Example 7 of the present specification, where methoxy PEG amines were synthesized using the methoxy PEG-OH of the invention and commercial methoxy PEG-OH. In any event, claims 7-15 require the high purity oxirane derivative of claim 1 as a starting material, which none of the prior art relied upon by the Examiner can provide. Thus, even if one of ordinary skill were to apply Kemp's technique to Martinez et al or JP '343, the inventive oxirane derivative still could not be obtained.

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I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Mar. 12, 2002


Chika Itoh